Remarks

Claims 2 to 14 and 16 to 17 are pending in the present patent application. Claims 1 and 15 have been canceled, without prejudice.

Discussion of the Rejection under 35 U.S.C. § 112, First Paragraph

Claims 2 to 7, 12 to 14, 16 and 17 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement with regard to the treatment of pain with compounds represented by the formula I or Ia (Action at 3). The Examiner contends that only the treatment of arthritis pain with N-[(S)-2-diphenylamino-2-(5-oxo-4,5-dihydro[1,3,4]oxadiazol-2-yl)ethyl]-2-(2-methylaminopyrimidin-4-yl-1H-indole-5-carboxamide is enabled (*id.*). Applicants traverse this rejection because one skilled in the art at the time of the present invention, having read the present specification and claims, would be able to make and use the present invention without engaging in undue experimentation.

The first paragraph of § 112 requires that the disclosure of a patent application be such that persons skilled in the art, having read the patent application, would be able to practice the inventions described by the claims (*In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988)). There is no legal requirement that this be done in any particular manner. An enabling disclosure can be provided by the use of illustrative examples or simply by broad terminology (*In re Marzocchi*, 169 U.S.P.Q. 367 (C.C.P.A. 1971)). The test of enablement is ***not*** simply whether experimentation would have been necessary, but whether such experimentation would have been ***undue*** (*see In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*see Wands*, 8 U.S.P.Q.2d at 1404). The factors to be considered in determining whether any necessary experimentation is undue include:

i. the breadth of the claims;
ii. the nature of the invention;
iii. the state of the prior art;
iv. the level of one of ordinary skill;
v. the level of predictability in the art;
vi. the amount of direction provided by the inventor;
vii. the existence of working examples; and
viii. the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

(id. (*citing Ex parte Forman*, 230 U.S.P.Q. 546, 547 (Bd. Pat. App. & Int. 1986)). Any conclusion of non-enablement must be based on the evidence as a whole (*id.*).

When rejecting a claim under the enablement requirement of § 112, first paragraph, the Patent Office bears the "initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification" (*In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993)). To object to an applicants' disclosure on the grounds that it is not enabling with respect to the scope of a claim sought to be patented, the Action must identify evidence or technical reasoning supporting any doubts regarding applicants' enablement of the claim (*id.*; MPEP § 2164.04). Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling (*In re Wright*, 27 U.S.P.Q.2d at 1513; *In re Marzocchi*, 169 U.S.P.Q. at 369).

Despite the Action's assertion that those skilled in the art would need to engage in undue experimentation to utilize "compounds represented by the formula I or Ia" "for treating pain" (Action at 3), there is no evidence or technical reason provided to support any contention that those of ordinary skill would have any difficulty in using the compounds of claim 1 to treat pain or that, if experimentation ***were*** required, such experimentation would not be routine in nature. For the reasons detailed below, Applicants submit respectfully that consideration of the *Wands* factors indeed demonstrates that those skilled in the art would be able to treat pain without engaging in undue experimentation.

The Level of the Skill in the Art

The level of skill in the relevant art is high such as, for example, a person having a Ph.D. in medicinal chemistry with experience in drug development. The remaining factors should be considered in view of the high level of skill in the art.

The Nature of the Invention and the Predictability in the Art

According to the Action, the nature of Applicants' invention is a "method of treatment of pain with IkB-kinase inhibitor compounds represented by the formula I or Ia" (Action at 4). The Action asserts that "pharmacological activity in general is a very unpredictable area" and as "there are no known compounds of similar structure which have been demonstrated to treat all types of pain . . . proof must be provided" (Action at 4). The Action, however, provides no evidence or technical reasoning in support of such statement other than an

unsupported assertion that such compounds are generally recognized in the art as being distinct from each other because of their diverse chemical structures. Such compounds, however, have been recognized in the art as sharing at least one common chemical property, namely inhibition of IkB-kinase (*see* U.S. Patent No. 6,358,978 to Ritzeler). One of ordinary skill in the art thus has the knowledge that these particular compounds may have the same chemical properties despite their diverse chemical structures.

The Presence or Absence of Working Examples

The Action asserts that the specification "has not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the (instantly claimed) compounds" (Action at 4). In direct contrast to this statement, the Action then asserts that "there is no demonstrated correlation that the tests and results apply to all of the compounds of disease conditions associated with pain embraced by the instant claims" (Action at 5). The specification does, in fact, contain working examples. In particular, N-[(S)-2-diphenylamino-2-(5-oxo-4,5-dihydro[1,3,4]oxadiazol-2-yl)ethyl]-2-(2-methylaminopyrimidin-4-yl-1H-indole-5-carboxamide (compound 13) and N-[((S)-1-carbamoyl-2-diphenylaminoethyl)-2-(2-methylaminopyrimidin-4-yl)-1H-benzimidazole-5-carboxamide (compound 22) are tested for pain alleviation (p. 35 to 39). The Action provides ***no evidence or technical reasoning*** as to why these working examples allegedly do not enable the claimed invention.

Applicants' claims also do not require a specific degree of treatment. The Action has not provided any evidence or technical reasoning to demonstrate that any of the compounds would ***not*** have some pain alleviating activity that results in ***some degree*** of treatment. Moreover, even if such differences in activities were present and required those of ordinary skill in the art to engage in ***some*** experimentation (*arguendo*), the Action has not provided any evidence or technical reasoning to show that such experimentation would be ***undue***. Thus, the Action has failed to demonstrate that Applicants' working examples are insufficient to enable the claimed invention.

The Amount of Direction or Guidance Present

The present specification provides ample disclosure to enable the claimed invention. The Action, however, asserts that "the specification does not provide sufficient guidance in how to use vast number of possible compounds represented by the formulas, other than compound 13" (Action at 6). Applicants, however, are not aware that a certain number of such examples are required to enable the claimed invention. There is no legal requirement

that enablement is accomplished in any particular manner and that an enabling disclosure can be provided by the use of illustrative examples or simply by broad terminology. *In re Marzocchi*, 169 U.S.P.Q. 367 (C.C.P.A. 1971). Accordingly, Applicants' disclosure demonstrating that compounds 13 and 22 inhibit pain provides ample guidance to those skilled in the art to allow practice of the claimed invention without undue experimentation.

The Breadth of the Claims & Quantity of Experimentation Needed

The Action alleges that the quantity of experimentation needed is undue, in part, because one skilled in the art would need to determine which of the "vastly different" compounds would treat pain, and whether such compounds can in fact treat a "wide range of pain" (Action at 5 to 6). The Action also alleges that there is no demonstrated correlation between the working examples such that all of the compounds or treatment of all disease conditions associated with pain are enabled (Action at 5). But as detailed above, Applicants' specification does provide enablement with respect to certain of the claimed compounds in the working examples. With respect to the remaining compounds, the burden is on the Examiner to provide ***some evidence or technical reasoning*** to show that one of ordinary skill in the art would not be able practice the claimed invention without undue experimentation in view of the teachings of the specification as a whole. As the Federal Circuit noted, for example:

> The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable to determination of how to practice a desired embodiment of the claimed invention.

PPG Indus., Inc. v. Guardian Indus. Corp, 37 U.S.P.Q.2d 1618, 1623 (Fed. Cir. 1996) (quotation and citation omitted). With regard to the enablement determination, the following statement from *In re Marzocchi*, 169 U.S.P.Q. 367, 369-70 (C.C.P.A. 1971), is noteworthy:

> The only relevant concern of the Patent Office under these circumstances should be over the truth of any assertion. The first paragraph of §112 requires nothing more than objective enablement. How such a teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in

> compliance with the enabling requirements of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support.

The law thus requires that the Patent Office accept Applicants' assertions of enablement or provide reasoning and evidence to substantiate doubts of the objective truth of Applicants' assertions. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (C.C.P.A. 1974); *In re Bowen*, 181 U.S.P.Q. 48 (C.C.P.A. 1974). The Action has provided no reason to doubt the truth of Applicants' teachings with respect to the claimed methods.

Thus, for all of the reasons detailed above, Applicants' claims are fully enabled by the present disclosure; one skilled in the art would not have to engage in undue experimentation to practice any of the claimed methods. Accordingly, reconsideration and withdrawal of the rejection are requested respectfully.

Discussion of the Rejection under 35 U.S.C. § 103(a)

Claims 2 to 14, 16 and 17 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable in view of U.S. Patent No. 6,358,978 to Ritzeler et al. ("Ritzeler"). Applicants respectfully traverse this rejection as one of ordinary skill in the art at the time of the present invention would not have been motivated to modify the teachings of Ritzeler in such a way as to administer the disclosed compounds to treat pain.

Applicants' claimed invention differs from Ritzeler in at least two respects. First, Ritzeler does not teach or suggest that any of compounds disclosed therein are useful to treat pain. Second, the compounds that are recited in the present method claims are a subgenus of those disclosed by Ritzeler. The MPEP is clear that "to establish a *prima facie* case of obviousness in a genus-species chemical composition situation … it is essential that Office personnel find some motivation or suggestion to make the claimed invention in light of the prior art teachings" (MPEP § 2144.08 II. A. at page 2100-153). Moreover, the MPEP is clear that in order to find such motivation or suggestion, "there should be a reasonable likelihood that the claimed invention would have the properties disclosed by the prior art teachings" (id). Applicants submit respectfully that Ritzeler is incapable of providing the requisite art-suggested motivation to select Applicants' claimed subgenus for use in Applicants' claimed methods.

Ritzeler discloses substituted benzimidazoles for use in the prevention or treatment of disorders, such as Alzheimer's disease, asthma, cachexia, psoriasis and multiple sclerosis, for example, in which increased activity of NFkB is involved (*see* Abstract). IkB kinase

activates NFkB which, in turn, activates proinflammatory genes that result in such disorders when NFkB is overactivated (*see* Col. 1, lines 8 to 32). The compounds of Ritzeler thus prevent the overactivation of NFkB via inhibiting IkB kinase (*see* Col. 1, lines 33 to 39).

In the first instance, the Action indeed provides ***no evidence*** or technical reasoning as to why one of ordinary skill in the art at the time of the present invention and presented with Ritzeler would select Applicants recited ***subgenus***. *In re Deuel*, 51 F.3d 1552, 34 USPQ.2d 1210 (CAFC 1995) (some motivation to select the claimed species or subgenus must be taught by the prior art). The absence of such evidence alone is enough to warrant withdrawal of the rejection.

Moreover, to the extent that the Action alleges that Ritzeler does provide the requisite motivation or suggestion to use the compounds that make up the claimed subgenus to ***treat pain***, the Action bases its allegation on an assumption that is plainly false. For example, the Action relies on the assumption that administering the presently claimed compounds to alleviate inflammation will "usually" alleviate pain (Action at 8). This position, however, assumes that pain is ***always*** associated with inflammation. Pain, however, is not always a characteristic of inflammation.

Referring to Exhibit A attached hereto, although pain may be associated with acute inflammatory conditions, pain is not necessarily associated with non-acute conditions (*see* Exhibit A, affirmatively stating that acute inflammatory conditions are recognized as being characterized by pain; however, the reference is notably silent with respect to whether non-acute inflammatory conditions are indeed characterized by pain). Moreover, certain of the diseases treated in Ritzeler that involve inflammation are not generally associated with pain, namely Alzheimer's disease, asthma, cachexia, psoriasis and multiple sclerosis. This indeed undermines the Actions allegations of reasonable expectation of success (assuming, *arguendo*, that the motivation is present in the first instance (which it is not)).

Thus, the Action's assumption that inflammation and pain go hand-in-hand is demonstrably incorrect. Accordingly, because Ritzeler is incapable of suggesting Applicants' recited subgenus for the treatment of pain, reconsideration and withdrawal of the rejection is requested respectfully.

Conclusion

Applicants respectfully submit that this application is now in condition for allowance. Accordingly, an indication of allowability and an early Notice of Allowance are respectfully requested. If there are any issues that can be resolved by a telephone conference or an Examiner's amendment, the Examiner is invited to call the undersigned attorney at (908) 231-3410.

The Commissioner is hereby authorized to charge the fee required and any additional fees that may be needed to Deposit Account No. **18-1982** in the name of Aventis Pharmaceuticals Inc.

Respectfully submitted,

Dated: September 29, 2006

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producing infection; pertaining to or characterized by the presence of pathogens.

infectivity (in″fek-tiv′ĭ-te) infectiousness.

infecundity (in″fe-kun′dĭ-te) [L. *infecunditas*] sterility or barrenness.

inferent (in′fer-ent) afferent.

inferior (in-fēr′e-or) [L. "lower"; neut. *inferius*] situated below, or directed downward; [NA] a term used in reference to the lower surface of an organ or other structure, or to the lower of two (or more) similar structures.

inferiority (in-fēr″e-or′ĭ-te) the condition of being inferior. **constitutional psychopathic i., psychopathic i.** (*obs.*), see *antisocial personality disorder*, under *personality*.

inferolateral (in″fer-o-lat′er-al) [L. *inferus* low + *latus* side] situated below and to one side.

inferomedian (in″fer-o-me′de-an) [L. *inferus* low + *medius* middle] situated in the middle of the under side.

inferonasal (in″fer-o-na′zal) [L. *inferus* low + *nasal*] in ophthalmology, that quadrant of the eye or of the visual field inferior to the horizontal meridian of the eye and medial to the vertical meridian.

inferoposterior (in″fer-o-pos-tēr′e-or) situated below and behind.

inferotemporal (in″fer-o-tem′por-al) [L. *inferus* low + *temporal*] in ophthalmology, that quadrant of the eye or of the visual field inferior to the horizontal meridian of the eye and lateral to the vertical meridian.

infertile (in′fer-til) not fertile; exhibiting infertility.

infertilitas (in″fer-til′ĭ-tas) [L.] infertility.

infertility (in″fer-til′ĭ-te) [L. *in* not + *fertilis* fruitful, prolific] diminished or absent capacity to produce offspring; the term does not denote complete inability to produce offspring as does *sterility*. Called also *relative sterility*. **primary i.,** infertility occurring in patients who have never conceived. **secondary i.,** infertility occurring in patients who have previously conceived.

infestation (in-fes-ta′shun) parasitic attack or subsistence on the skin and its appendages, as by insects, mites, or ticks; sometimes used to denote parasitic invasion of the tissues or organs, as by helminths because helminths are larger than bacteria, viruses, and protozoa, and unlike the case with infection by those organisms, do not multiply within the body.

infibulation (in-fib-u-la′shun) [L. *infibulare* to buckle together] the act of buckling, or fastening as if with buckles, especially the chiefly abandoned practice of fastening the prepuce or labia minora together with clasps, stitches, or other devices to prevent coitus. Cf. *pharaonic circumcision*, under *circumcision*.

infiltrate (in-fil′trāt) 1. to penetrate the interstices of a tissue or substance. 2. material deposited by infiltration. **Assmann's tuberculous i.,** see under *focus*.

infiltration (in″fil-tra′shun) [L. *in* into + *filtration*] the diffusion or accumulation in a tissue or cells of substances not normal to it or in amounts in excess of the normal. Also, the material so accumulated. Cf. *degeneration*. **adipose i.,** fatty i. **calcareous i.,** a deposit of lime and magnesium salts in the tissues. **calcium i.,** a deposit of calcium salts within the tissues of the body. **cellular i.,** the migration and accumulation of cells within the tissues. **epituberculous i.,** a collateral hyperemia and inflammatory infiltration surrounding a tuberculous focus. **fatty i.,** 1. a deposit of fat in the tissues, especially between the cells. 2. the presence of fat vacuoles in the cytoplasm of cells, as occurs in fatty change in the liver, myocardium, and kidneys. **gelatinous i.,** gray i. **glycogen i.,** abnormal accumulations of glycogen within the cytoplasm of cells, as occurs in diabetes mellitus and the glycogen storage diseases. **gray i.,** a condition of the lungs in acute tuberculosis in which, after death, they assume a gray appearance; called also *gelatinous i.* **inflammatory i.,** that formed by an inflammatory exudation penetrating the interstices of a tissue. **lymphocytic i. of skin,** a manifestation of cutaneous lymphoid hyperplasia, occurring most often in men, characterized by the appearance of asymptomatic, single or multiple, firm, reddish papules or plaques that expand peripherally to form circinate lesions, sometimes with central clearing; the lesions may be induced or aggravated by light exposure. **paraneural i.,** paraneural anesthesia. **sanguineous i.,** infiltration with extravasated blood. **serous i.,** the abnormal presence of lymph in a tissue. **tuberculous i.,** the formation of a group or of groups of tuberculous cells and bacilli in a tissue. **urinous i.,** extravasation of urine into a tissue.

infirm (in-firm′) [L. *infirmis; in* not + *firmus* strong] weak; feeble, as from disease or old age.

infirmary (in-fir′mah-re) [L. *infirmarium*] a hospital or place where sick or infirm persons are maintained or treated; commonly used to denote a space or a building set aside for the care of members of a group or community; a dispensary.

infirmity (in-fir′mĭ-te) [L. *infirmitas*] 1. a feeble or weak state of the body or mind. 2. a disease or condition producing weakness.

inflammagen (in-flam′ah-jen) an irritant that elicits both edema and the cellular response of inflammation. Cf. *edemagen*.

inflammation (in″flah-ma′shun) [L. *inflammatio; inflammare* to set on fire] a localized protective response elicited by injury or destruction of tissues, which serves to destroy, dilute, or wall off (sequester) both the injurious agent and the injured tissue. It is characterized in the acute form by the classical signs of pain (dolor), heat (calor), redness (rubor), swelling (tumor), and loss of function (functio laesa). Histologically, it involves a complex series of events, including dilatation of arterioles, capillaries, and venules, with increased permeability and blood flow; exudation of fluids, including plasma proteins; and leukocytic migration into the inflammatory focus. **acute i.,** inflammation, usually of sudden onset, characterized by the classical signs (see *inflammation*), in which the vascular and exudative processes predominate. **adhesive i.,** that which promotes the adhesion of contiguous surfaces. **atrophic i.,** a form which results in atrophy and deformity. **catarrhal i.,** a form which affects principally a mucous surface, and which is marked by a copious discharge of mucus and epithelial debris. **chronic i.,** inflammation of slow progress and marked chiefly by the formation of new connective tissue; it may be a continuation of an acute form or a prolonged low-grade form, and usually causes permanent tissue damage. **cirrhotic i.,** atrophic i. **croupous i.,** a fibrinous inflammation leading to the formation of a false membrane. **diffuse i.,** one that is both interstitial and parenchymatous or is spread over a large area. **disseminated i.,** one that has a number of distinct foci. **exudative i.,** one in which the prominent feature is an exudate. **fibrinous i.,** one that is characterized by an exudate of coagulated fibrin. **fibroid i.,** atrophic i. **focal i.,** one that is confined to a single spot or to a few limited spots. **granulomatous i.,** an inflammation, usually chronic, characterized by the formation of granulomas; see also *granuloma*. **hyperplastic i.,** one which leads to the formation of new connective tissue fibers. **hypertrophic i.,** inflammation marked by increase in the size of the elements composing the affected tissue. **interstitial i.,** one that primarily affects the stroma of an organ. **metastatic i.,** one that is reproduced in a distant part by the conveyance of infectious material through the blood vessels and lymph organs. **necrotic i.,** inflammation attended by death of the affected tissue. **obliterative i.,** inflammation of the lining membrane of a cavity or vessel, producing adhesions between the surfaces and consequent obliteration of the lumen. **parenchymatous i.,** one that primarily affects the essential tissue elements of an organ. **plastic i., productive i., proliferous i.,** hyperplastic i. **pseudomembranous i.,** an acute inflammatory response to a powerful necrotizing toxin, such as the diphtheria toxin, characterized by the formation on a mucosal surface, most often in the pharynx, larynx, respiratory passages, and intestinal tract, of a false membrane composed of precipitated fibrin, necrotic epithelium, and inflammatory white cells. **purulent i.,** suppurative i. **sclerosing i.,** atrophic i. **seroplastic i.,** inflammation accompanied by both serous and plastic exudation. **serous i.,** one which produces an exudation of serum. **simple i.,** that in which there is no flow of pus or other product of inflammation. **specific i.,** one that is due to a particular microorganism. **subacute i.,** a condition intermediate between chronic and acute inflammation, exhibiting some of the characteristics of each. **suppurative i.,** one characterized by the formation of pus. **toxic i.,** one that is caused by a poison, such as a bacterial product. **traumatic i.,** one that is caused by an injury. **ulcera-**

tive i., that in which necrosis on or near the surface leads to loss of tissue and creation of a local defect (ulcer).

inflammatory (in-flam′ah-to″re) pertaining to or characterized by inflammation.

inflation (in-fla′shun) [L. *in* into + *flare* to blow] 1. distention with air, gas, or a fluid. 2. the act of distending with air or with a gas.

inflator (in-fla′tor) an instrument for inflating any organ for therapeutic or diagnostic purposes.

inflection, inflexion (in-flek′shun) [L. *inflexio; in* in + *flectere* to bend] the act of bending inward or the state of being bent inward, as of a limb.

inflorescence (in″flo-res′ens) the structure or arrangement of the flowers of a plant.

influenza (in″flu-en′zah) [Ital. "influenza"] an acute viral infection involving the respiratory tract, occurring in isolated cases, in epidemics, or in pandemics striking many continents simultaneously or in sequence. It is marked by inflammation of the nasal mucosa, the pharynx, and conjunctiva, and by headache and severe, often generalized myalgia. Fever, chills, and prostration are common. Involvement of the myocardium and of the central nervous system occur infrequently. A necrotizing bronchitis and interstitial pneumonia are prominent features of severe influenza and account for the susceptibility of patients to secondary bacterial pneumonia due to *Streptococcus pneumoniae, Haemophilus influenzae,* and *Staphylococcus aureus.* The incubation period is one to three days and the disease ordinarily lasts for three to ten days. Influenza is caused by a number of serologically distinct strains of virus, designated A (with many subgroups), B, and C. Called also *flu* and *grippe* (*grip*). See also *influenza virus,* under *virus.* **i. A,** the most common variety of influenza caused by the type A strain of influenza virus; epidemics of this form occur at two- to three-year intervals. The causative strain is subject to wide variations in antigenic type, called antigenic shift, and outbreaks of influenza A caused by such antigenic types have been called *Asian i., Spanish i., Russian i.,* and so on. See *influenza virus,* under *virus.* **Asian i.,** a pandemic of influenza A occurring in 1957, thought to originate in China. **avian i.,** Newcastle disease. **i. B,** a variety of influenza caused by the type B strain of influenza virus; epidemics of this form occur at four- to five-year intervals. See *influenza virus,* under *virus.* **i. C,** a variety of influenza occurring sporadically and caused by the type C strain of influenza virus. See *influenza virus,* under *virus.* **endemic i.,** infection with influenza virus occurring continuously within a population, i.e., between epidemics, either sporadically and not recognized as influenza or as a clinically inapparent infection. **equine i.,** a highly contagious febrile respiratory disease of horses caused by two immunologically distinct strains of influenza virus A. **feline i.,** a name loosely applied to any of a group of highly contagious viral infections of the respiratory tract in cats. **goose i.,** infectious avian serositis in geese. **Hong Kong i.,** a pandemic of influenza A occurring in 1968, thought to originate in Hong Kong. **laryngeal i.,** influenza in horses in which pharyngitis is the chief symptom. **Russian i.,** a pandemic of influenza A occurring in 1978, thought to originate in the U.S.S.R. **Spanish i.,** a name given to the acute influenza-like disease, a pandemic of which passed over Europe and America during the summer and autumn of 1918. **swine i.,** a highly contagious disease of hogs caused by simultaneous infection with *Haemophilus influenzae* and a virus.

influenzal (in″flu-en′zal) pertaining to influenza.

infolding (in-fōld′ing) 1. the folding inward of a layer of tissue, as in the formation of the neural tube in the embryo. 2. the enclosing of redundant tissue by suturing together the walls of the organ on either side of it.

informosome (in-for′mo-sōm) a name suggested for the combination of mRNA and protein found in the cytoplasm of eukaryotic cells.

infra- [L. *infra* beneath] a prefix meaning below or beneath.

infra-axillary (in″frah-ak′sĭ-lār″e) below the axilla.

infrabulge (in′frah-bulj) the surfaces of a tooth gingival to the height of contour, or sloping cervically; the surface of the crown of a tooth cervical to the clasp guideline or surveyed height of contour, being the retention area of a tooth. Cf. *suprabulge.*

infraciliature (in″frah-sil′ĭ-ah-chur) [*infra-* + *cilium*] the basal bodies and kinetodesmata of ciliate protozoa considered collectively.

infraclass (in′frah-klas) a taxonomic category sometimes established, subordinate to a subclass and superior to an order.

infraclavicular (in″frah-klah-vik′u-lar) beneath a clavicle.

infraclusion (in″frah-kloo′zhun) malocclusion in which a tooth has failed to erupt fully and reach the line of occlusion and is out of contact with the opposing tooth. Called also *infraversion.*

infraconstrictor (in″frah-kon-strik′tor) the inferior constrictor of the pharynx.

infracortical (in″frah-kor′tĭ-kal) beneath the cortex, as of the brain.

infracostal (in″frah-kos′tal) [*infra-* + L. *costa* rib] below a rib or below the ribs.

infracotyloid (in″frah-kot′ĭ-loid) beneath the cotyloid cavity or acetabulum.

infraction (in-frak′shun) [L. *in* into + *frac'tio* break] incomplete fracture of a bone without displacement of the fragments. **Freiberg's i.,** osteochondrosis of the head of the second metatarsal bone.

infradentale (in″frah-den-ta′le) an osteometric landmark, being the highest anterior point on the gingiva between the mandibular central incisors.

infradian (in″frah-de′an, in-fra′de-an) [*infra-* + L. *dies* day] pertaining to the rhythmic repetition of certain phenomena in living organisms occurring in cycles of less frequency than circadian, that is, less frequently than once a day. Cf. *circadian* and *ultradian.*

infradiaphragmatic (in″frah-di″ah-frag-mat′ik) below the diaphragm.

infraduction (in″frah-duk′shun) [*infra-* + *duction*] 1. the downward rotation of an eye around its horizontal axis. 2. the downward rotation of one eye independent of the other by a baseup prism in testing for vertical divergence. See also *infravergence* and *infraversion.* Called also *deorsumduction* and *subduction.*

infraglenoid (in″frah-gle′noid) below the fossa of the glenoid cavity.

infraglottic (in″frah-glot′ik) below the glottis.

infrahyoid (in″frah-hi′oid) below the hyoid bone.

inframamillary (in″frah-mam′ĭ-lār″e) below the nipple.

inframammary (in″frah-mam′ah-re) below the mammary gland.

inframandibular (in″frah-man-dib′u-lar) beneath the lower jaw.

inframarginal (in″frah-mar′jĭ-nal) situated below a margin or border.

inframaxillary (in″frah-mak′sĭ-lār″e) beneath the upper jaw (maxilla).

infranuclear (in″frah-nu′kle-ar) below a nucleus.

infraorbital (in″frah-or′bĭ-tal) lying under or on the floor of the orbit.

infrapatellar (in″frah-pah-tel′ar) below the patella.

infrapsychic (in″frah-si′kik) below the psychic level; automatic.

infrared (in-frah-red′) denoting thermal radiation of wavelength greater than that of the red end of the visible spectrum, between the red waves and the radio waves, having wavelengths between 0.75 and 1000 μm. Infrared rays emanating from tissues are the basis of thermography. **far i., long-wave i.,** infrared radiation of the longest wavelength, i.e., furthest from the visible spectrum (wavelength about 3.0 to 1000 μm.). **near i., short-wave i.,** infrared radiation of the shortest wavelength, i.e., closest to the visible spectrum (wavelength about 0.75 to 3.0 μm.).

infrascapular (in″frah-skap′u-lar) beneath the scapula.

infrasonic (in″frah-son′ik) below the frequency range of the waves normally perceived as sound by the human ear.

infraspinous (in″frah-spi′nus) beneath the spine of the scapula.

infrasternal (in″frah-ster′nal) below the sternum.

infrastructure (in″fra-struk′chur) substructure, def. 2. **implant i.,** see under *substructure.*